Part I. A CONVENIENT SYNTHESIS OF *dl*-METHIONINE

Part II. *w*, *w'*-BIMETHIONINE

BY

GEORGE WESLEY CANNON

A.B., Dakota Wesleyan University, 1939
M.S., University of Illinois, 1941

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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PART I. A CONVENIENT SYNTHESIS OF *dl*-METHIONINE

Introduction

Since methionine is the only essential amino acid containing sulfur it has been of particular interest in nutrition studies; consequently there has been a need for the racemic amino acid for use in these studies. Three syntheses of *dl*-methionine have been described. Those of Windus and Marvel[1] and of Barger and Weichselbaum[2] have been used most extensively, but they possess numerous undesirable features. The synthesis of Hill and Robson[3] uses α-benzamino-γ-butyrolactone, a compound which has been difficult to prepare.

The present work was undertaken in an effort to devise a synthetic method which would permit a more economical preparation of *dl*-methionine from the readily available α-aceto-γ-butyrolactone.

Discussion

A convenient and economical synthesis of *dl*-methionine has been developed. The over-all yield, calculated on the basis of α-aceto-γ-butyrolactone, is 26-37%. Each intermediate is used without purification, and the product does not contain an impurity (See Part II) found in the methionine prepared by the procedure of Barger and Weichselbaum.[2] The hazards of older syntheses which employed β-chloroethyl methyl sulfide are eliminated.

The new synthesis involves the following steps:

1) The conversion of α-aceto-γ-butyrolactone to α-oximino-γ-butyrolactone (I), m.p. 187-188°, in 85-91 per cent yields, by treatment with ethyl nitrite. The reaction is catalyzed by traces of hydrogen chloride.

2) Catalytic reduction of the oxime (I) in methanol solution with palladium chloride-charcoal catalyst to α-amino-γ-butyrolactone which is not isolated but is allowed to dimerize to 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (II), m.p. 186-187.5°. The yield of the diketopiperazine, based on the oxime, is 55-67 per cent. This yield is not improved by addition of hydrogen chloride, acetic acid, or ammonia to the reduction

solution.

3) Conversion of the dihydroxydiketopiperazine (II) to 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (III), m.p. 230-231°, in 90-95 per cent yields, by the action of thionyl chloride.

4) The quantitative formation of 3,6-*bis*-(β-isothiouroniumethyl)-2,5-diketopiperazine chloride (IV), m.p. 255°, by allowing a mixture of thiourea and the dichlorodiketopiperazine (III) in absolute ethanol to boil under reflux for twenty-four hours.

5) The quantitative conversion of the diisothiouronium salt (IV) to 3,6-*bis*-(β-methylthiolethyl)-2,5-diketopiperazine (V) by the slow addition of a sodium hydroxide solution to a mixture of the diisothiourium salt (IV), dimethyl sulfate, and water at 0°

6) Hydrolysis of the crude methionine anhydride (V) to *dl*-methionine, in 65 per cent yield, by heating under reflux with concentrated hydrochloric acid. The crude anhydride (V) could be crystallized to give a 75 per cent yield of a pure product which gives 85-95 per cent yields of *dl*-methionine.

An alternative procedure for steps 4 and 5 was developed in which the dichlorodiketopiperazine (III) was converted directly to methionine anhydride (V), m.p. 231-232°, by heating under reflux in absolute ethanol with sodium methyl mercaptide. This material was of sufficient purity to give 85-95 per cent yields of *dl*-methionine.

Bibliography

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PART II. *w,w'*-BIMETHIONINE

Introduction

"Pseudomethionine" is the name given an impurity which was found in the *dl*-methionine obtained when the procedure of Barger and Weichselbaum[1] was adapted to the large-scale preparation of the amino acid.[2] It is impossible to free the

methionine of all traces of the contaminant, the composition of which is so near that of methionine that ordinary analysis does not reveal its presence.

The isolation of "pseudomethionine" was of especial interest inasmuch as methionine made by the Barger-Weichselbaum procedure has been used in nutrition studies. The purpose of the present work was to determine the structure of "pseudomethionine" and, if possible, to synthesize the material for physiological studies.

Theory and Discussion

Analytical data and the chemical behavior of "pseudomethionine"[2] indicated that the substance is composed of two molecules of methionine linked together through carbon atoms by the loss of two hydrogen atoms.

Autoalkylation of β-chloroethyl methyl sulfide may give rise to polysulfonium and monosulfonium halides. Decomposition of either of these sulfonium salts would lead to the formation of the same product, ethylene *bis*-(β-chloroethyl sulfide). In the Barger - Weichselbaum synthesis this dichloride would give rise to ω,ω′-bimethionine, an amino acid of the same composition as "pseudomethionine." The experimental conditions used in the Barger-Weichselbaum synthesis are those which would favor the formation and decomposition of sulfonium chlorides.

ω, ω′-Bimethionine was prepared by the procedure of M. A. Nyman[3] by treating ethylene *bis*-(β-chloroethyl sulfide) with ethyl acetaminomalonate followed by hydrolysis and decarboxylation. Color tests and the melting points (285-288°) of ω, ω′-bimethionine and "pseudomethionine" were indistinguishable.

Derivatives of the two samples were prepared in an effort to confirm their identity. Benzoyl "pseudomethionine", m.p. 157-160°, and benzoyl ω, ω′-bimethionine, m.p. 145-154°, were prepared; a mixture of the two melted at 155-160° Formyl "pseudomethionine", m.p. 114-154°, and formyl ω,ω′-bimethionine, m.p. 171-174°, were prepared; a mixture of the two melted at 160-168° Analyses of each of these derivatives was in excellent agreement with the proposed structure. Their behavior

may be ascribed to the presence of mixtures of the *dl*- and the *meso*- forms.

Reductive cleavage over Raney nickel of *dl*-ethylene *bis*-[β-(3-phenyl-5-hydantoin)ethyl sulfide], m.p. 155-164°, obtained from "pseudomethionine," and of *dl*-3-phenyl-5-(β-methylthiolethyl) hydantoin, obtained from *dl*-methionine, gave the same compound, 3-phenyl-5-ethylhydantoin, m.p. 122-122.5°. The isolation of this substance from "pseudomethionine" demonstrates the presence of $-SCH_2CH_2CH(NH_2)COOH$ groups in the molecule. If the complete structure is $[-CH_2SCH_2CH_2CH(NH_2)COOH]_2$, the other product expected from the cleavage is ethane. However, analysis of the gas liberated during the reaction revealed the presence of methane and ethane (44-56%). The gas from the reductive cleavage of "pseudomethionine" itself contained both methane and ethane (54-66%) also. Reductive cleavage of dithioglycol and 1,2-(diphenylthiol)-ethane likewise gave both methane and ethane (44-56% and 23-77%, respectively). The normal cleavage products of compounds containing the group $-CH_2SCH_2CH_2S-CH_2-$ are thus methane and ethane, and the assignment of the structure of ω,ω′bimethionine to "pseudomethionine" is further justified.

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3. M. A. Nyman, private communication.

VITA

The writer was born in Dickey, North Dakota on January 22, 1917. He graduated from the Woonsocket, South Dakota, high school in May 1935. In September of that same year he matriculated at Dakota Wesleyan University, where he was granted the Bachelor of Arts degree in June 1939. In the fall of 1939 he entered the Graduate School of the University of Illinois, where he held a teaching assistantship from 1939 to 1942 and a University Fellowship during the academic year 1942-1943.

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